Omeprazole vs famotidine for the prevention of gastroduodenal injury in high-risk users of low-dose aspirin: A randomized controlled trial

Zhi-Fu Tseng[a], Ping-I Hsu[b], Nan-Jing Peng[c], Sung-Shuo Kao[a], Feng-Woei Tsay[a], Jin-Shiung Cheng[a], Wen-Chi Chen[a], Kun-Feng Tsai[b], Sheng-Yeh Tang[b], Seng-Kee Chuah[d], Chang-Bih Shie[b,*]

[a]Division of Gastroenterology and Hepatology, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC; [b]Division of Gastroenterology and Hepatology, Department of Internal Medicine, An Nan Hospital, China Medical University, Tainan, Taiwan, ROC; [c]Department of Nuclear Medicine, Kaohsiung Veterans General Hospital and National Yang-Ming University, Kaohsiung, Taiwan, ROC; [d]Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC

Abstract

Background: Low-dose aspirin is widely used in the prevention of cardiovascular diseases. However, the use of aspirin is associated with an increased risk of gastrointestinal injury.

Methods: Low-dose aspirin users with a history of peptic ulcers who did not have gastroduodenal mucosal breaks at initial endoscopy were randomly assigned to receive famotidine (20 mg bid) or omeprazole (20 mg qd) for 6 months. Follow-up endoscopy was performed at the end of the sixth month and whenever epigastric discomfort, hematemesis, or melena occurred. The primary end point was the occurrence of gastroduodenal mucosal breaks. The secondary end points were (1) the occurrence of gastroduodenal ulcers and (2) the occurrence of gastroduodenal bleeding.

Result: Between November 2013 and June 2018, 170 patients were randomly assigned to receive either famotidine (n = 84) or omeprazole (n = 86). The incidence of gastroduodenal mucosal breaks was 33.8% among the patients receiving famotidine, and 19.8% among those receiving omeprazole (95% CI: 0.4%-27.5%; $p = 0.045$). The two patient groups had comparable incidence rates of gastroduodenal ulcers (20.0% vs 9.8%; $p = 0.071$), and gastroduodenal bleeding (2.5% vs 0%; $p = 0.243$). Multivariate analysis showed that use of the proton pump inhibitor was an independent protective factor (odds ratio: 0.47; 95% CI: 0.23-0.99; $p = 0.047$), and that smoking was a risk factor for mucosal breaks (odds ratio: 3.84; 95% CI: 1.52-9.71; $p = 0.004$).

Conclusion: Proton pump inhibitor was superior to histamine-2 receptor antagonist in the prevention of gastroduodenal mucosal breaks in high-risk users of low-dose aspirin, and smoking was an independent risk factor for developing gastroduodenal mucosal breaks.

Keywords: Peptic ulcer; Prevention & control; Smoking

1. INTRODUCTION

Low-dose aspirin, defined as 75 to 325 mg daily, is widely used for the primary and secondary prevention of cardiovascular events. Currently, approximately 36% of the adult US population is estimated to take aspirin regularly for cardiovascular protection.[1] However, due to its inhibition of prostaglandin synthesis, direct cytotoxicity, and microvascular injury, aspirin is associated with upper gastrointestinal side effects ranging from troublesome symptoms to life-threatening peptic ulcer bleeding, perforation, and even death.[2,3]

Both upper gastrointestinal symptoms and gastroduodenal erosions are very common in low-dose aspirin users. The point prevalence rates of upper gastrointestinal symptoms and gastroduodenal erosions in low-dose aspirin users are approximately 31% and 60%, respectively.[4,5] Most of low-dose aspirin-related peptic ulcers are asymptomatic.[6] A prospective study demonstrated that the 12-week cumulative incidence of endoscopic ulcers in low-dose aspirin users was 7%.[7] Patients taking low-dose aspirin had two- to fourfold higher risk of serious ulcer complications than control.[4] A large 5-year observational cohort study from Denmark showed that the annual incidence of hospitalization for upper gastrointestinal bleeding in low-dose aspirin users was 0.6% per year.[8]

Acid inhibitors have been widely used to prevent gastrointestinal complications in low-dose aspirin users. Taha et al[9] reported that histamine-2 receptor antagonists (H2RAs) were effective in the prevention of gastric and duodenal ulcers, and erosive esophagitis in patients taking low-dose aspirin. In addition, a previous meta-analysis demonstrated that proton pump

** Address correspondence. Dr. Chang-Bih Shie, Division of Gastroenterology and Hepatology, Department of Internal Medicine, An Nan Hospital, China Medical University, 66, Section 2, Changhe Road, Tainan 709, Taiwan, ROC. E-mail address: D73890@mail.tmanh.org.tw (C.-B. Shie).*

Author Contributions: Dr. Zhi-Fu Tseng and Dr. Ping-I Hsu contributed equally to this study.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 19-24.

Received April 20, 2020; accepted July 23, 2020.

doi: 10.1097/JCMA.0000000000000465.

inhibitors (PPIs) were also effective in preventing peptic ulcers, erosive esophagitis, and dyspeptic symptoms without increasing adverse events, cardiac risk, or mortality in long-term aspirin users.[10] A recent randomized controlled trial found that vonoprazan, a novel potassium-competitive acid blocker, was as effective as lansoprazole in preventing peptic ulcer recurrence during low-dose aspirin therapy, and that it had a similar long-term safety profile and was well tolerated.[11]

Whether PPIs are superior to H2RAs in reducing the risk of gastrointestinal mucosal breaks, peptic ulcer, or upper gastrointestinal bleeding in high-risk users of low-dose aspirin remains controversial. In addition, the risk factors for gastrointestinal injury in low-dose aspirin users receiving co-therapy with acid inhibitors remain to be clarified. The aims of this study were (1) to investigate whether PPI is superior to H2RA in the prevention of mucosal breaks in high-risk users of low-dose aspirin and (2) to identify the risk factors for mucosal breaks in high-risk low-dose aspirin users receiving co-therapy with PPI or H2RA.

2. METHODS

2.1. Study population

Patients who underwent endoscopy survey for dyspepsia or other complaints who had a past history of bleeding or non-bleeding gastroduodenal ulcer proven by endoscopy at our hospital and took aspirin to prevent cerebral and cardiovascular events were screened. They were recruited for the study if they met the following criteria: initial endoscopic examination revealed normal appearance or pictures of gastritis only; they required long-term use of low-dose aspirin (75-325 mg) for cerebral or cardiovascular events; and they were adult patients aged >20 years. Patients were excluded if they had a history of gastric or duodenal surgery other than oversewing of a perforation; if they were allergic to omeprazole or famotidine; if their glomerular filtration rate <30 mL/min/1.73 m2; if they were pregnant; if they had active cancer, acute serious medical illness, or terminal illness; if they had *Helicobacter pylori* infection; if they have gastroesophageal reflux disease; and if they required long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulant agents, or thienopyridine (eg, clopidogrel and ticlopidine). The patients taking other antiplatelet agents (eg, persantin) were not excluded from this study. All patients received rapid urease test to assess *H pylori* status on screening endoscopy. Those with *H pylori* infection were excluded. The trial was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (No.: VGHKS13-CT10-11) in 2013.

2.2. Design

The eligible patients were randomly assigned to receive either (1) famotidine (20 mg bid) or (2) omeprazole (20 mg qd) for 24 weeks. Randomization was performed with the use of a computer-generated list of random numbers. An independent staff member assigned the treatments according to consecutive numbers that were kept in sealed envelopes. Anticoagulants, cyclooxygenase-2 inhibitors, conventional NSAIDs, misoprostol, and sucralfate were prohibited. The administration of an antacid (Iwell, Everest, Taiwan) was permitted for the control of dyspeptic symptoms. Compliance with the regimen was assessed by counting the pills that were returned.

2.3. Follow-up

Patients were followed up as outpatients with visits every 2 months. Gastrointestinal and cardiovascular symptoms were assessed at each visit. They were asked to return to the outpatient clinic if they had persistent dyspeptic symptoms (epigastric pain, fullness, nausea, or vomiting) and visited the emergency room if they had evidences of gastrointestinal bleeding (hematemesis, melena, or sudden onset of severe epigastric pain), cardiovascular events (chest pain, syncope, or sudden onset of severe palpitation), or cerebrovascular accidents (conscious disturbance, hemiparesis, or dysphagia). Follow-up endoscopy was performed whenever persistent dyspepsia, severe epigastric pain, hematemesis, or melena occurred and at the end of the sixth month. The endoscopists who performed follow-up endoscopy were unaware of the treatment group assignments.

2.4. End points

The primary end point was the incidence of gastroduodenal mucosal break. The secondary end points were (1) the incidence of peptic ulcer and (2) the incidence of gastroduodenal bleeding. A gastroduodenal mucosal break was defined as a well-defined mucosal loss in the stomach or duodenum. A peptic ulcer was defined as a circumscribed mucosal break at least 0.3 cm in diameter (measured using endoscopy forceps) and with a perceptible depth in the stomach or duodenum.[12] Gastroduodenal bleeding was defined as hematemesis or melena documented by the admitting physician, with ulcers/erosions bleeding in the stomach or duodenum confirmed on endoscopy, or a decrease in the hemoglobin level of at least 2 g/dL in the presence of endoscopically documented peptic ulcers or erosions in the 6-month study period.[13] Poor drug compliance was defined as taking <80% of pills.

2.5. Statistical Analysis

Chi-square test with or without Yates correction for continuity and Fisher's exact test were used when appropriate to compare the outcomes between groups. SPSS software (version 10.1, Chicago, IL, USA) was used for all statistical calculations. A p value of <0.05 was considered statistically significant. All p values were two-sided. Before conducting the study, we had retrospectively reviewed the endoscopic findings of 20 patients with low-dose aspirin use and famotidine co-therapy for at least 6 months. Additionally, the endoscopic findings of 20 low-dose aspirin users who received omeprazole co-therapy for at least 6 months were also investigated. The point incidences of gastroduodenal mucosal breaks in these patients with co-therapy by famotidine and omeprazole were 35.0% and 15.0%, respectively. We therefore estimated that at the end of 6 months, the primary end point (development of gastroduodenal mucosal break) would occur in 35% of patients in the famotidine group and 15% of patients in the omeprazole group. It was estimated that we required a minimum of 81 patients in each treatment group to demonstrate an absolute difference of 20% with a type I error of 0.05 and a type II error of 0.2 in two sided tests, assuming 15% loss to receive follow-up endoscopy. Analysis was by intention-to-treat (ITT) and per-protocol (PP). The ITT population included all randomized patients who receive at least one dose of study drug and underwent follow-up endoscopy. The PP analysis excluded the patients who had poor drug compliance.

To determine the independent factors affecting the development of gastroduodenal mucosal break, clinical parameters were analyzed by univariate analysis. These variables include the following: age (<60 or ≥60 years); gender, history of smoking, history of alcohol consumption (<80 or ≥80 g/d); ingestion of coffee (<1 cup/d or ≥1 cup/d); ingestion of tea (<1 cup/d or ≥1 cup/d); and type of acid inhibitor (PPI or H2RA). Those variables found to be significant by univariate analysis were subsequently assessed by a stepwise logistic regression method to identify independent factors for the development of gastroduodenal mucosal break.

3. RESULTS

3.1. Patients

Between November 2013 and June 2018, we screened 202 consecutive patients who had a past history of gastroduodenal ulcers and received long-term low-dose aspirin treatment, of whom 170 were recruited. They were randomly assigned to receive famotidine (n = 84) or omeprazole (n = 86). Among them, 80 patients in the famotidine group and 81 patients in the omeprazole group undergoing follow-up endoscopy were included for ITT analysis. In the 161 patients receiving follow-up endoscopy, 4 patients in the famotidine group and 3 patients in the omeprazole group were excluded from PP analysis because of poor drug compliance (taking <80% of pills; Fig. 1). Overall, 76 patients in the famotidine group and 78 patients in the omeprazole group were included in the PP analysis. On enrollment, the two groups of patients had comparable age; gender; history of smoking; alcohol, coffee, and tea consumption; history of recent NSAID use; concomitant steroid use; type 2 diabetes mellitus; liver cirrhosis; and cerebral vascular disease (Table 1). Fig. 1 summarizes the patient disposition.

3.2. Gastrointestinal injury

Among the patients receiving follow-up endoscopy, 27 subjects in the famotidine group (n = 80) and 16 subjects in the omeprazole group (n = 81) developed gastroduodenal mucosal breaks

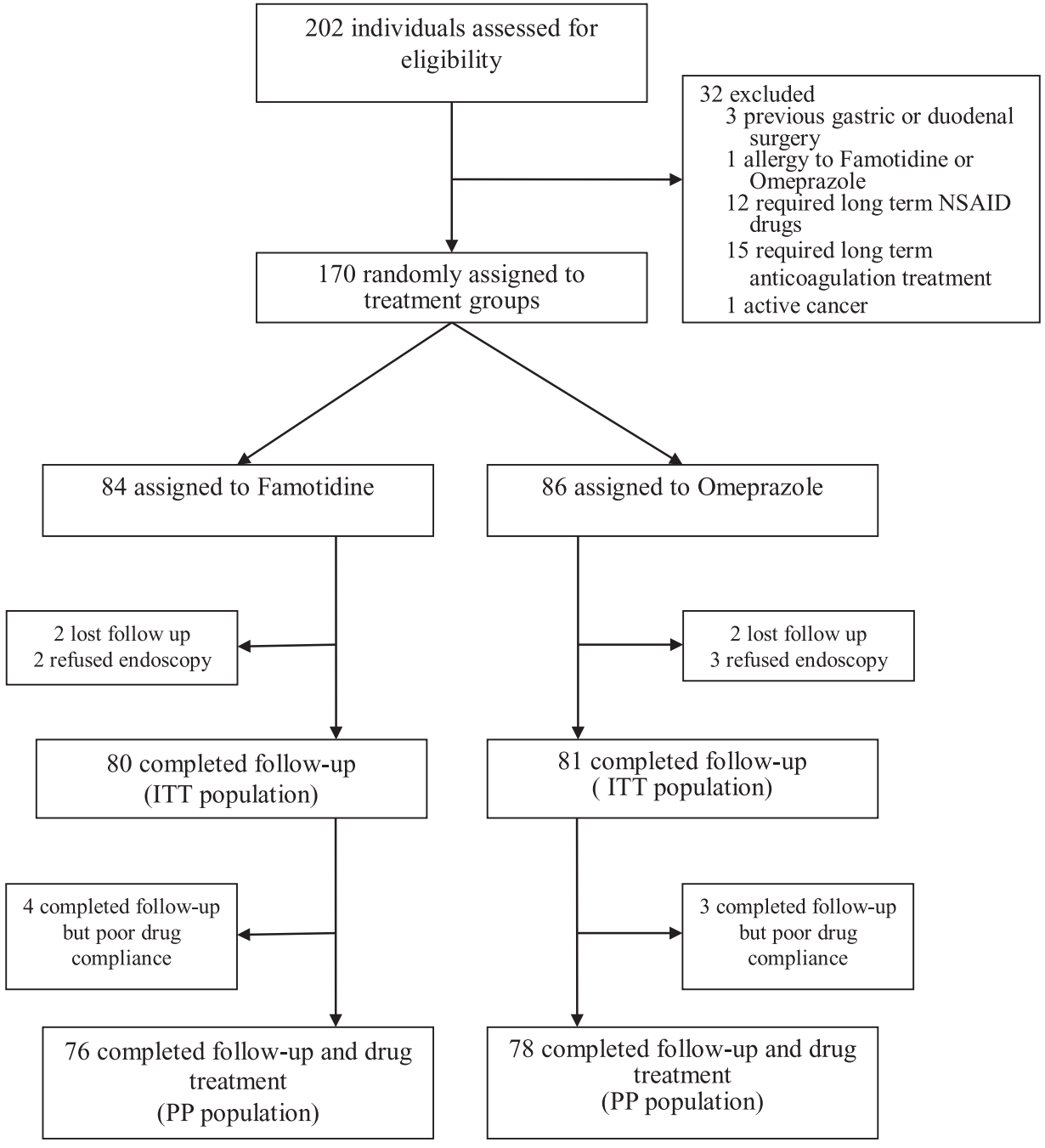

Fig. 1 Disposition of patients. ITT = intention-to-treat; NSAID = nonsteroidal anti-inflammatory drug; PP = per-protocol.

Table 1

Demographic data of patients (n =170)

Characteristics	Famotidine (n = 84)	Omeprazole (n = 86)	*p*
Age, y (mean ± SD)	68.3 ± 9.5	67.6 ± 10.9	0.665
Sex			0.662
Female	25 (29.8%)	23 (26.7%)	
Male	59 (70.2%)	63 (73.3%)	
Smoking			0.886
(–)	71 (84.5%)	72 (83.7%)	
(+)	13 (15.5%)	14 (16.3%)	
Alcohol drinking			0.441
(–)	80 (95.2%)	84 (97.7%)	
(+)	4 (4.8%)	2 (2.3%)	
Ingestion of coffee			0.615
(–)	71 (84.5%)	75 (87.2%)	
(+)	13 (15.5%)	11 (17.2%)	
Ingestion of tea			0.326
(–)	73 (86.9%)	70 (81.4%)	
(+)	11 (13.1%)	16 (18.6%)	
Recent non aspirin NSAID use			1.000
(–)	83 (98.8%)	85 (98.8%)	
(+)	1 (1.2%)	1 (1.2%)	
Concomitant steroid			1.000
(–)	84 (100%)	85 (98.8%)	
(+)	0 (0%)	1 (1.2%)	
Coronary artery disease			0.828
(–)	46 (54.8%)	47 (54.7%)	
(+)	38 (45.2%)	39 (45.3%)	
Cerebrovascular disease			0.596
(–)	73 (86.9%)	77 (89.5%)	
(+)	11 (13.1%)	9 (10.5%)	
Chronic obstructive lung disease			1.000
(–)	84 (100%)	85 (98.8%)	
(+)	0 (0%)	1 (1.2%)	
Liver cirrhosis			1.000
	83 (98.2%)	86 (100%)	
	1 (1.1%)	0 (0%)	
Type 2 diabetes mellitus			0.828
(–)	46 (54.8%)	48 (55.8%)	
(+)	38 (45.2%)	38 (44.2%)	

NSAID = nonsteroidal anti-inflammatory drugs.

(Table 2). ITT analysis showed that the famotidine group had a higher incidence of gastroduodenal mucosal breaks than the omeprazole group (33.8% vs 19.8%; difference: 14.0%; 95% CI: 0.4%-27.5%; p = 0.045). In the patients with good drug adherence, PP analysis demonstrated similar results (35.5% vs 20.5%; difference: 15.0%; 95% CI: 0.9%-29.0%; p = 0.038; Table 2). Among the patients with gastroduodenal mucosal breaks shown in follow-up endoscopy, nine patients (33.3%) in the famotidine group (n = 27) and five patients (31.3%) in the omeprazole group (n = 16) did not report symptoms.

Among the patients receiving follow-up endoscopy, gastroduodenal ulcer occurred in 16 subjects (20.0%) receiving famotidine prophylaxis and in 8 subjects (9.8%) receiving omeprazole prophylaxis. ITT analysis revealed that the famotidine group had a slightly higher incidence of gastroduodenal ulcers than the omeprazole group, although this difference was not statistically significant in ITT analysis (difference: 10.2%; 95% CI: -0.6% to 21.0%; p = 0.071; Table 2). Peptic ulcer bleeding occurred in two patients (2.5%) in the famotidine group, but in none of the patients (0%) in the omeprazole group. There was no significant difference in the incidence of peptic ulcer bleeding between the two groups (p = 0.243).

Table 2

Clinical outcomes of the patients receiving famotidine or omeprazole for the second prevention of aspirin-related gastrointestinal injury

Gastrointestinal injury	Famotidine group	Omeprazole group	*p* (95% CI)
Gastroduodenal mucosal break			
Intention-to-treat analysis	27/80 (33.8%) (23.4% to 44.2%)	16/81 (19.8%) (11.1% to 28.5%)	0.045
Per-protocol analysis	27/76 (35.5%) (24.7% to 46.3%)	16/78 (20.5%) (11.4% to 29.5%)	0.038
Gastroduodenal ulcer			
Intention-to-treat analysis	16/80 (20.0%) (11.2% to 28.8%)	8/81 (9.8%) (3.33% to 16.3%)	0.071
Per-protocol analysis	16/76 (21.1%) (11.9% to 30.3%)	8/78 (10.3%) (3.55% to 17.0%)	0.065
Gastroduodenal bleeding			
Intention-to-treat analysis	2/80 (2.5%) (–0.9% to 5.9%)[a]	0/81 (0%)	0.471
Per-protocol analysis	2/76 (2.6%) (–0.9% to 6.2%)[a]	0/78 (0%)	0.465

[a]Values represent CI.

3.3. Independent risk factors predicting the development of gastroduodenal mucosal break in high-risk users of low-dose aspirin

Univariate analysis revealed that PPI use and history of smoking were the two factors associated with the development of gastroduodenal mucosal break (p = 0.045 and 0.022, respectively; Table 3) in low-dose aspirin users with a history of peptic ulcer. Multivariate analysis showed that PPI use was an independent protective factor (odds ratio: 0.47; 95% CI: 0.23-0.99; p = 0.047) for the development of mucosal breaks. In contrast, smoking was an independent risk factor predicting the development of gastroduodenal mucosal break (odds ratio: 3.84; 95% CI: 1.52-9.71; p = 0.004) in high-risk users of low-dose aspirin (Table 4).

4. DISCUSSION

Low-dose aspirin is widely used because it reduces the risk of CV events and death in patients with coronary and cerebrovascular diseases and has the advantages of both low cost and long duration of antiplatelet action. However, low-dose aspirin therapy is associated with upper gastrointestinal side effects, which range from dyspepsia (point prevalence: 31%), gastroduodenal erosions (point prevalence: 60%), endoscopic peptic ulcer (3-month incidence: 7%) to symptomatic or complicated ulcers (annual incidence of upper gastrointestinal bleeding: 0.6%; relative risk of upper gastrointestinal bleeding: 2.6).[14,15] The FAMOUS (Famotidine for the Prevention of Ulcers in Users of Low-dose Aspirin) trial documented that H2RA is effective in the prevention of peptic ulcers and erosive esophagitis in patients taking low-dose aspirin.[9] In this study, we tested the hypothesis that PPI is superior to H2RA in the prevention of gastroduodenal mucosal break among low-dose aspirin users with a peptic ulcer history. The data showed that 33.8% of low-dose aspirin users with a peptic ulcer history who received famotidine prophylaxis still had a higher incidence of gastroduodenal mucosal break during a 6-month follow-up period. The high-risk users of low-dose aspirin users receiving co-therapy with omeprazole had a lower incidence of gastroduodenal mucosal break (19.8%) than those receiving famotidine prophylaxis. Multivariate analysis verified that PPI use was an independent protective factor for the development of gastroduodenal mucosal break in low-dose

Table 3

Univariate analysis for the risk factors of gastroduodenal mucosal breaks in high-risk users of low-dose aspirin

Characteristics	Number of patients (n = 161)[a]	Gastroduodenal mucosal breaks (n = 43)	*p*
Age, y			0.478
<60	28	9 (32.1%)	
≥60	133	34 (25.5%)	
Sex			0.922
Female	44	12 (27.3%)	
Male	117	31 (26.4%)	
Smoking			0.022
(–)	138	31 (22.5%)	
(+)	23	12 (52.2%)	
Alcohol drinking			0.218
(–)	156	40 (25.6%)	
(+)	5	3 (60.0%)	
Ingestion of coffee			0.949
(–)	139	37 (26.6%)	
(+)	22	6 (27.3%)	
Ingestion of tea			0.323
(–)	135	34 (25.2%)	
(+)	26	9 (34.6%)	
Recent NSAID use			0.457
(–)	159	42 (26.4%)	
(+)	2	1 (50.0%)	
Concomitant steroid			1.000
(–)	160	43 (26.9%)	
(+)	1	0 (0 %)	
PPI			0.045
(–)	80	27 (33.8%)	
(+)	81	16 (19.8%)	

NSAID = nonsteroidal anti-inflammatory drugs; PPI = proton pump inhibitors.
[a]Only patients receiving follow-up endoscopy were included in the analysis.

Table 4

Multivariate analysis for the independent risk factors of gastroduodenal mucosal breaks in high-risk users of low-dose aspirin

Clinical factor	Coefficient	SE	Odds ratio (95% CI)	*p*
PPI use	–0.747	0.377	0.47 (0.23-0.99)	0.047
Smoking	1.345	0.473	3.84 (1.52-9.71)	0.004

PPI = proton pump inhibitors.

aspirin users with an odds ratio of 0.47 (95% CI: 0.23-0.99). The data confirm our hypothesis that PPI is more effective than H2RA in the prevention of gastroduodenal mucosal break in low-dose aspirin users who have a peptic ulcer history.

In the current study, the omeprazole group had a lower incidence of gastroduodenal ulcers than the famotidine group (9.8% vs 20.0%); however, the difference was not statistically significant (p = 0.071). A recent randomized controlled trial by Chan et al also demonstrated that high-risk users of low-dose aspirin receiving PPI had slightly lower recurrent bleeding and ulcers than those receiving low-dose aspirin and an H2RA (7.9% vs 12.4%), although these difference were also not statistically significant (p = 0.26).[16] With regard to upper gastrointestinal bleeding, a case-control study by Lanas et al revealed that, compared with patients undergoing antiplatelet therapy without protective co-therapy, H2RAs could significantly reduce the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin.[17] Although the current study and the randomized controlled trial by Chan et al showed similar efficacy of PPIs and H2RAs in reducing the risk of upper gastrointestinal bleeding in high-risk users of low-dose aspirin, a randomized controlled trial by Ng et al demonstrated that gastrointestinal bleeding was significantly more common in high-risk users of low-dose aspirin receiving famotidine than in those receiving pantoprazole (7.7% vs 0%).[16,18]

The reported risk factors for upper gastrointestinal injury induced by low-dose aspirin include a history of bleeding peptic ulcers, prior peptic ulcers, age >70 years, *H pylori* infection, and concomitant drug therapy with NSAIDs, other antiplatelet agents (eg, thienopyridine), or anticoagulants.[4,8,19] In the current study, we found that smoking was an independent risk factor for the development of gastroduodenal mucosal breaks in in our patients with an odds ratio of 3.84 (95% CI: 1.52-9.71; p = 0.004). Previous studies have reported that smoking is associated with the pathogenesis of peptic ulcer disease.[20–22] Uemura et al[23] also showed that smoking was a significant risk factor for peptic ulcers, although the exact mechanisms of smoking-related gastroduodenal injury remains unclear. Previous studies have shown that smoking can increase gastric acid secretion, decrease bicarbonate secretion,[24–27] and cigarette smoke is also known to be a significant generator of reactive oxygen species.[28] Tobacco smoke comprised >7000 chemical compounds and oxidative agents, and it contains 10^{14} to 10^{16} free radicals per puff.[29] The reactive oxidative species induced by smoking may also contribute to the development of gastrointestinal mucosal injury.[30]

Our study had several limitations. First, some of the patients did not receive follow-up endoscopy. The patients without symptoms who refused follow-up endoscopy were regarded as no gastroduodenal lesions. Since gastroduodenal mucosal breaks or peptic ulcer may be asymptomatic, the number of gastroduodenal mucosal breaks or ulcer in this study might be underestimated in both groups. Second, our findings relate only to low-dose aspirin monotherapy and that this is not generalizable to most patients taking dual antiplatelet therapy (low-dose aspirin plus clopidogrel).

In conclusion, PPI is superior to H2RA in the prevention of gastroduodenal mucosal break in low-dose aspirin users with a peptic ulcer history. Smoking is an independent risk factor for the developing gastroduodenal mucosal breaks in high-risk users of low-dose aspirin.

REFERENCES

1. Ajani UA, Ford ES, Greenland KJ, Giles, WH, Mokdad AH. Aspirin use among U.S. adults. *Am J Prev Med* 2006;**30**:74–7.
2. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. *BMJ* 1990;**300**:278–84.
3. Hsu PI. New look at antiplatelet agent-related peptic ulcer: an update of prevention and treatment. *J Gastroenterol Hepatol* 2012;**27**:654–61.
4. Yeomans ND, Lanas AI, Talley NJ, Thomson AB, Daneshjoo R, Eriksson B, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharmacol Ther* 2005;**22**:795–801.
5. Simon B, Elsner H, Muller P. Protective effect of omeprazole against low dose acetylsalicylic acid. Endoscopic controlled double-blind study in healthy subjects. *Arzneimittelforshung* 1995;**45**:701–3. [In German, English abstract].
6. Niv Y, Battler A, Abuksis G, Gal E, Sapoznikov B, Vilkin A. Endoscopy in asymptomatic minidose aspirin consumers. *Dig Dis Sci* 2005;**50**:78–80.
7. Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. *Gastroenterology* 2004;**127**:395–402.
8. Sørensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000;**95**:2218–24.

9. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet* 2009;**374**:119–25.
10. Dahal K, Sharma SP, Kaur J, Anderson BJ, Singh G. Efficacy and safety of proton pump inhibitors in the long-term aspirin users: a meta-analysis of randomized controlled trials. *Am J Ther* 2017;**24**:e559–69.
11. Kawai T, Oda K, Funao N, Nishimura A, Matsumoto Y, Mizokami Y, et al. Vonoprazan prevents low-dose aspirin-associated ulcer recurrence: randomised phase 3 study. *Gut* 2018;**67**:1033–41.
12. Tsai TJ, Lai KH, Hsu PI, Lin CK, Chan HH, Yu HC, et al. Upper gastrointestinal lesions in patients receiving clopidogrel anti-platelet therapy. *J Formos Med Assoc* 2012;**111**:705–10.
13. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. *Gastroenterology* 2011;**140**:791–8.
14. Hsu PI, Tsai TJ. Epidemiology of upper gastrointestinal damage associated with low-dose aspirin. *Curr Pharm Des* 2015;**21**:5049–55.
15. Tsai TJ, Hsu PI. Low-dose aspirin-induced upper gastrointestinal injury—epidemiology, management and prevention. *J Blood Disord Transfus* 2015;**6**:327.
16. Chan FK, Kyaw M, Tanigawa T, Higuchi K, Fujimoto K, Cheong PK, et al. Similar efficacy of proton-pump inhibitors vs H2-receptor antagonists in reducing risk of upper gastrointestinal bleeding or ulcers in high-risk users of low-dose aspirin. *Gastroenterology* 2017;**152**:105–110.e1.
17. Lanas A, García-Rodríguez LA, Arroyo MT, Bujanda L, Gomollón F, Forné M, et al.; Investigators of the Asociación Española de Gastroenterología (AEG). Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am J Gastroenterol* 2007;**102**:507–15.
18. Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. *Gastroenterology* 2010;**138**:82–8.
19. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sáinz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther* 2002;**16**:779–86.
20. Jedrychowski W, Popiela T. Association between the occurrence of peptic ulcers and tobacco smoking. *Public Health* 1974;**88**:195–200.
21. Friedman GD, Siegelaub AB, Seltzer CC. Cigarettes, alcohol, coffee and peptic ulcer. *N Engl J Med* 1974;**290**:469–73.
22. Gillies MA, Skyring A. Gastric and duodenal ulcer. The association between aspirin ingestion, smoking and family history of ulcer. *Med J Aust* 1969;**2**:280–5.
23. Uemura N, Sugano K, Hiraishi H, Shimada K, Goto S, Uchiyama S, et al.; MAGIC Study Group. Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. *J Gastroenterol* 2014;**49**:814–24.
24. Massarrat S. Smoking and gut. *Arch Iran Med* 2008;**11**:293–305.
25. Massarrat S, Enschai F, Pittner PM. Increased gastric secretory capacity in smokers without gastrointestinal lesions. *Gut* 1986;**27**:433–9.
26. Murthy SN, Dinoso VP Jr, Clearfield HR, Chey WY. Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretin during smoking. *Gastroenterology* 1977;**73**(4 Pt 1):758–61.
27. Murthy SN, Dinoso VP Jr, Clearfield HR, Chey WY. Serial pH changes in the duodenal bulb during smoking. *Gastroenterology* 1978;**75**:1–4.
28. Halliwell B, Cross CE. Oxygen-derived species: their relation to human disease and environmental stress. *Environ Health Perspect* 1994;**102**(Suppl 10):5–12.
29. Yang SR, Valvo S, Yao H, Kode A, Rajendrasozhan S, Edirisinghe I, et al. IKK alpha causes chromatin modification on pro-inflammatory genes by cigarette smoke in mouse lung. *Am J Respir Cell Mol Biol* 2008;**38**:689–98.
30. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiol Rev* 2014;**94**:329–54.